IN THE BOARD OF APPEALS AND INTERFERENCES
OF THE UNITED STATES PATENT & TRADEMARK OFFICE

12/ Appeal Brief (3)

On Appeal of the Final Rejection
dated April 15, 2003 in the matter of:

Applicant:	KUMAR et al.	Technology Center: 1600
Application No.:	09/888,268	Examiner: Micah Paul Young
Filing Date:	June 22, 2001	Group Art Unit: 1615
For:	BIOAVAILABLE DOSAGE FORM OF LORATADINE	

Bet 10-14-03

BRIEF ON APPEAL

Mail Stop Appeal Brief – Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

1. Real Party in Interest

The real party in interest in this case is Ranbaxy Laboratories Limited, the Assignee of the present application, the assignment being recorded at Reel 012269, Frame 0767.

2. Related Appeals and Interferences

There are no appeals and/or interferences related to this case.

3. Status of Claims

Claims 1-18 are pending in the application (see Appendix)

Claims 1-18 have been finally rejected in the application.

4. Status of Amendments

No amendment has been filed subsequent to the Final Office Action.

5. Summary of Invention

It is an objective of the present invention to provide a bioavailable oral dosage form of loratadine, that is bioequivalent to the commercially available formulation and falls within the prescribed limits set by various International Regulatory Agencies. Accordingly, the present invention provides a bioavailable oral dosage form of loratadine, comprising reduced particle size loratadine, such that the average particle size ranges from about 0.1 microns to 15 microns and the average surface area falls between 1 and 2 m^2/g. The particle size of the drug is reduced thereby increasing its surface area using any of the conventional milling techniques known in the art. These include the use of ball mill, cad mill, multi mill, air jet mill etc.

6. Issues

The rejection of claims 1-18 rejected under 35 U.S.C. 103(a) as being unpatentable over Ayer et al. (U.S. Patent No. 3,980,778) in view of Vilkov et al. (U.S. Patent No. 5,807,579).

7. Grouping of Claims

All the claims appealed herein stand or fall together.

Argument

The rejection of claims 1-18 as unpatentable over Ayer et al. in view of the Vilkov et al. is improper.

According to the Examiner, Ayer discloses a drug formulation containing an active ingredient which can be an antihistamine and the active agent is ball milled to sizes below 5 microns. Vilkov discloses a pharmaceutical tablet containing loratadine. The Examiner asserts that one skilled in the art would have been motivated to incorporate the

loratadine of Vilkov into the formulation and process of Ayers. Applicants respectfully disagree because there is no suggestion or motivation in the combination of cited references to produce a dosage form of loratadine having a specific particle size and surface area as claimed.

Ayer teaches topical creams and ointments that include a steroid which has been "ball-milled with a little mineral oil to a particle size of less than 5 microns". See Examples A, C, and C1. As is known in the art, the particle size in a topical preparation must be sufficiently small to provide a smooth texture without the gritty feel of larger particles. Thus, Ayers is not ball-milling the steroids of Examples A, C, and C1 to improve their bioavailability but to provide the desired texture of a topical preparation. In fact, contrary to teaching particle size reduction to increase bioavailability or potency, Ayer states that the weight percentage of the steroid can be increased to raise the potency. See Col. 18, lines 50-52. No where does Ayer disclose or suggest to increase the surface area to increase the bioavailability.

Although Ayer teaches oral dosage forms, he does not teach oral dosage forms having a particle size that is less than 5 microns. While Ayer's Examples S and T are oral dosage forms with micronized active ingredient, Ayer does not disclose either a size range of the particles or a surface area of the particles. Instead, only the ointments and creams are stated to have a particle size of less than 5 microns. Thus, contrary to the assertion by the Examiner, Ayer lacks any disclosure or reference to the reduction of particle size and increase in surface area in order to increase the bioavailability. In summary, Ayer discloses oral dosage forms but does not disclose the particle size of the active ingredient in them. Although Ayer discloses the particle size of the active

ingredient being less than 5 microns in ointments and creams, one skilled in the art would not look to an ointment or cream to teach how to increase the bioavailability of the active ingredient in an oral dosage form.

The Examiner also asserts that the antihistamine would be ball-milled to a size of less than 5 microns. Again, Ayer discloses ball-milling to a particle size of less than 5 microns only in the context of a topical ointments or creams. One skilled in the art would not apply an antihistamine such as the loratadine of claim 1 via a topical ointment or cream. As stated by the Federal Circuit in Northern Telecom, Inc. v. Datapoint Corp., 908 F.2d 931, 15 USPQ2d 1321 (Fed.Cir.1990), "[i]t is insufficient that the prior art disclosed the components of the patented device, either separately or used in combinations; there must be some teaching, suggestion, or incentive to make the combination made by the inventor." Accordingly, Applicants respectfully submit that Ayer would not have taught one of skill in the art to make an oral dosage form of an antihistamine having the particle size range and surface area of claim 1.

Further, Ayer teaches the steroid only in combination with other active ingredients one of which is an antihistamine and Vilkov teaches pseudoephedrine in combination with antihistamines. Thus each of these references teaches that one particular active ingredient steroid and pseudoephedrine, respectively must be in the combination drug product. Accordingly, if there was a motivation to combine Ayer and Vilkov, one of skill in the art would be taught by Ayer to include a steroid and by Vilkov to include pseudoephedrine. Thus, the resulting formulation would be a combination drug of a steroid and pseudoephedrine rather than the loratadine of claim 1. "[I]t is impermissible to use the claimed invention as an instruction manual or 'template' to

piece together the teachings of the prior art so that the claimed invention is rendered obvious..." In re Fritch, 972 F.2d 1260, 23 USPQ2d 1780 (Fed.Cir.1992).

Alternatively, even if *prima facie* obviousness were established, the evidence of unexpected and superior results in bioavailability over the commercially available formulations of loratadine is sufficient to overcome the *prima facie* case (See Table 4.2, page 8 of the application as filed and is reproduced below).

Table 4.2

	$AUC_{(0-t)}$	$AUC_{(0-\alpha)}$	C_{max} (μg/ml)
Test/ Reference (%)	134	124	130

Considering that one skilled in the art would assume the expected bioavailability results to parallel the bioavailability of the commercial product, the present results are evidence of an unexpected and superior 30% increase above the commercial product. When weighed against the evidence supporting prima facie obviousness, this objective statistical improvement carries much greater weight. Since the claimed invention exhibits superior bioavailability, one skilled in the art would find these results unexpected or surprising. "[This] principle applies most often to the less predictable fields, such as chemistry, where minor changes in a product or process may yield substantially different results." In re Soni, 54 F.3d 746, 34 USPQ2d 1684 (Fed.Cir.1995). For this reason, as well as the arguments presented above, Applicants submit that claims 1-9 are patentable over Ayers in view of Vilkov.

Independent claim 10 is directed to a method of making an oral dosage form containing loratadine. Like claim 1, claim 10 recites a formulation of loratadine having a particle size of 0.1 to 15 microns and a surface area of 1 to 2.5 m^2/g. As such, claim 10

and dependent claims 11-18 are allowable over Ayer and Vilkov for the same reasons that claim 1 is allowable.

Conclusion

In light of the foregoing, Applicants submit that claims 1-18 are unobvious over Ayer in view of Vilkov.

Respectfully submitted,
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APPENDIX

WE CLAIM:

1. A bioavailable oral dosage form of loratadine comprising loratadine having an average particle size ranging from about 0.1 microns to about 15 microns and having a surface area ranging from between 1 and 2.5 m^2/g.

2. The bioavailable oral dosage form of claim 1, wherein the particle size of loratadine is between about 1 micron to about 10 microns.

3. The bioavailable oral dosage form of claim 1, wherein the surface area of loratadine is between 1.25 and 2.0 m^2/g.

4. The bioavailable oral dosage form of claim 1, wherein the drug is mixed with other pharmaceutically acceptable fillers, binders, and lubricants.

5. The bioavailable oral dosage form of claim 4, wherein the fillers used are selected from the group consisting of saccharides, polyhydric alcohols, celluloses, and cellulose ethers.

6. The bioavailable oral dosage form of claim 4, wherein the fillers are selected from the group consisting of lactose, dextrose, sucrose, microcrystalline celluloses, hydroxypropyl methyl cellulose, and mixtures thereof.

7. The bioavailable oral dosage form of claim 4, wherein the binders are selected from the group consisting of starch, polyvinylpyrrolidone, and gums.

8. The bioavailable oral dosage form of claim 4, wherein the lubricants are selected from the group consisting of talc, magnesium strearate, zinc stearate, tristearin, tripalmitin, polyethylene glycol, waxes, aerosil, and mixtures thereof.

9. The bioavailable oral dosage form of claim 1, wherein the dosage form is formulated as a tablet, capsule or suspension.

10. A process for the preparation of a bioavailable oral dosage form of loratadine comprising the step of milling said loratadine to reduce the particle size such that the average particle size ranges from about 0.1 microns to about 15 microns and the surface area ranges from between 1 and 2.5 m^2/g.

11. The process as described in claim 10, wherein the particle size of loratadine is between about 1 micron to about 10 microns.

12. The process as described in claim 10, wherein the surface area of loratadine is between 1.25 and 2.0 m^2/g.

13. The process as described in claim 10, wherein the milled drug is mixed with other pharmaceutically acceptable fillers, binders, and lubricants.

14. The process as described in claim 13, wherein the fillers used are selected from the group consisting of saccharides, polyhydric alcohols, celluloses, and cellulose ethers.

15. The process as described in claim 13, wherein the fillers are selected from the group consisting of lactose, dextrose, sucrose, micro-crystalline celluloses, hydroxypropyl methyl cellulose, and mixtures thereof.

16. The process as described in claim 13, wherein the binders are selected from the group consisting of starch, polyvinylpyrrolidone, and gums.

17. The process as described in claim 13, wherein the lubricants are selected from the group consisting of talc, magnesium strearate, zinc stearate, tristearin, tripalmitin, polyethylene glycol, waxes, aerosil, and mixtures thereof.

18. The process as described in claim 10, wherein the dosage form is formulated as a tablet, capsule or suspension.